

REMARKS

Reconsideration and allowance of this application is respectfully requested in view of the following remarks.

Claim Status

Claims 1-13, 16 and 18 are pending. Claims 1-2, 8 and 11 were amended. Claims 14, 15, 19 and 20 are withdrawn. Claim 17 is canceled. No new matter was added.

35 USC §112

Claims 11 and 12 stand rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant traverses.

Claim 11 has each been amended to depend from claim 10, which depends from claim 8, which has been amended to depend from claim 2 which provides sufficient antecedent basis for the limitation "the product obtained by crystallization." Based on the amendments and the information outlined above, Applicant respectfully requests that the rejection be removed and the claims allowed.

35 USC §103

Claims 1, 3 and 6-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable under U.S. Patent No. 6,541,635 (hereinafter Tien). Applicant traverses.

Tien fails to establish a *prima facie* case of obviousness. MPEP §2143 "Basic Requirements of a *Prima Facie* Case of Obviousness" states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine references teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations.

Regarding the third criterion, the court has stated that "to establish *prima facie* obviousness of a claimed invention, **all** the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicant contends that Tien fails to teach, suggest, or provide a motivation for describing a method for preparing optionally substituted {N-[1-(S)-carbalkoxy-3-phenylpropyl]-S-alanyl-2S, 3aR, 7aS-octahydroindole-2-carboxylic acid} and pharmaceutically acceptable salts thereof containing all of the

claimed limitations from amended independent claims 1 or 2 of the instant invention.

The instant application refers to the reaction of a racemic mixture of *trans*-octahydroindole-2-carboxylic acid with the N-carboxyanhydride (NCA) of {N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine} (ECAPPA). This is contrary to what is described in Tien which requires the use of an acid in the ester form which is protected with a trialkylsilyl group (OSiMe₃). The use of this protection group is an essential feature of the invention described in Tien.

The prior art reference or combination of references relied upon by the Examiner must teach or suggest all of the limitations of the claims. See *In re Zurko*, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1467, 1478 (Fed. Cir. 1997); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). The teachings or suggestions, as well as the expectation of success, must come from the prior art, not applicant's disclosure. See *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). In this instance, from the information detailed above,

it is clear that Tien fails to teach or suggest all the limitations of claims 1 or 2 in the instant application.

The reaction of the N-carboxyanhydride (NCA) of {N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine} with the octahydroindole-2carboxylic acid specifically consists in the reaction of the NCA with the reactive hydrogen atom of the -NH- group of the octahydroindole-2carboxylic acid. To one skilled in the art it would be obvious that no other free reactive hydrogen atom should be present in the reaction mixture, and definitely not within the same molecule (i.e. within the octahydroindole-2carboxylic acid) to compete with the reactive hydrogen of the -NH- group and cause side reactions.

Additionally one skilled in the art would also find it obvious that no other free reactive hydrogen atom should be present in the reaction mixture to compete with the reactive hydrogen of the -NH- group and either partially inhibit or entirely inhibit the reaction between the NCA and the -NH- group. Therefore, those skilled in the art would know that the prior art has shown the free hydrogen atom of the carboxylic acid was always blocked, e.g. by adding a protective group to the carboxylic group, as described in Tien.

The Examiner argues on Page 6 of the current office action that, "it would be obvious to try to perform a well-known reaction that involves protecting groups without the use of the protecting group in order to shorten the reaction time." With all respect due to the Examiner, this argument is incorrect and is plainly based on hindsight reconstruction. If it would be obvious to carry out the reaction without any protective group, as is described in the instant application, then the obvious question is, why did Tien fail to describe this option. Tien does not teach, suggest, provide a motivation or contain any indication that the free, non-protected, octahydroindole-2carboxylic acid could be used in the manner described in the instant invention. To the contrary, Tien appears to teach away from the instant invention through its use of the special trialkylsoloxy protecting group in order to minimize the by-products and improve the yield and product purity. (Column 2, Lines 33-36).

Motivation may be lacking when the state of the art at the time of the invention in question was discovered pointed researchers in a different direction than the inventor proceeded. Indeed, the Federal Circuit has repeatedly recognized that proceeding contrary to the accepted wisdom in the art represents "strong evidence of unobviousness." *In re Hedges*,

783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) (prior art teaching that conventional polypropylene should have reduced crystallinity before stretching and should undergo slow stretching, led away from claimed process of producing porous article by expanding highly crystalline PTFE by rapid stretching); accord *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988). Clearly, in the instant case, there is a distinct lack of motivation based on its use of the protecting group trialkylsoloxy.

Additionally, the U.S. Supreme Court recently held that rigid and mandatory application of the "teaching-suggestion-motivation," or TSM, test is incompatible with its precedents. *KSR Int'l Co. v. Teleflex, Inc.* 127 S.Ct 1727, 1741 (2007). The Court did not, however, discard the TSM test completely; it noted that its precedents show that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.*

The Court held that the TSM test must be applied flexibly, and take into account a number of factors "in order to determine

whether there was an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1740-41. Despite this flexibility, however, the Court stated that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does." *Id.* "To facilitate review, this analysis should be made explicit." *Id.*

The obviousness rationale addressed in *KSR* was premised on combining elements known in the prior art. *Id.* at 1738-39. The *KSR* Court noted that obviousness cannot be proven merely by showing that the elements of a claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed." *Id.* at 1741.

In the same way, when the prior art teaches away from the claimed solution, obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition. See also *Ex parte Thomas J. Whalen II, et al*, BPAI 2007-4423 (2008).

Based on *KSR v. Teleflex, Inc.* 127 S.Ct. 1727, 167 L.Ed2d 705, 2007 U.S. Lexis 4745 (2007), the obviousness question may be broken down to: Is the invention predictable based upon the prior art? *Id.* at 1740, 721.

Simply, the answer to that question is "no." Hindsight reconstruction is not permitted as the Federal Circuit has repeatedly warned that the requisite motivation to modify a reference must come from the prior art, not Applicant's specification. See *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988) ("there must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure.") Using an Applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated piece of the prior art contravenes the statutory mandate of section 103 of judging obviousness at the point in time when the invention was made. See *Grain Processing Corp. v. American Maize-Prod. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988).

Only hindsight reconstruction based upon the instant specification would lead the Examiner to the conclusion that the claims in the instant application are rejected under §103 as

unpatentable over Tien. Accordingly, the instant rejection of independent claims 1 and 2 must be removed.

In reference to claims 3-13, 16 and 18, dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987); *In re Abele*, 684 F.2d 902, 910, 214 USPQ 682, 689 (CCPA 1982); see also *In re Sernaker*, 702 F.2d 989, 991, 217 USPQ 1, 3 (Fed. Cir. 1983). Thus, claims 3-13, 16 and 18 are not unpatentable over Tien and should be allowed.

An early Notice of Allowance is respectfully requested.

Respectfully submitted,



Blake E. Vande Garde
Attorney for Applicant
Registration No. 58,264

Customer No. 29494
Hammer & Associates, P.C.
3125 Springbank Lane
Suite G
Charlotte, NC 28226
Telephone: 704-927-0400
Facsimile: 704-927-0485
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